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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,085	05/11/2001	Akihiro Ishii	3007/49966	5264

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EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621
DATE MAILED: 01/13/2003 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/853,085	ISHII ET AL.
	Examiner Paul A. Zucker	Art Unit 1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 04 November 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-13 and 25-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-3,5-13,26 and 28 is/are rejected.

7) Claim(s) 4,25 and 27 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

Current Status

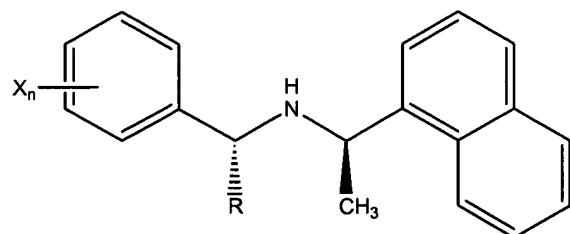
1. This action is responsive to Applicants' amendment of 4 November 2002 in Paper No 12.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Applicants' addition of new claims 25-28 is acknowledged.
4. Claims 1-13 and 25-28 remain pending.
5. The objection to the oath set forth in paragraph 2 of the previous Office Action in Paper No 11 is withdrawn in response to Applicants' remarks.
6. The rejections under 35 USC § 112, second paragraph, set forth in paragraphs 4 - 5 of the previous Office Action in Paper No 11 are withdrawn in response to Applicants' amendment of the claims.
7. Claims 1-3,5-9,12, 26 and 28 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Bringman et al (DE 3819438-A1 01-1989) and further in view of Van Wagenen et al (US 6,211,244-B1 04-2001).

The instantly claimed invention consists of the synthesis of an optically active phenyl-substituted phenethylamine via the formation of the imine (Schiff's base) via reaction of a ketone and optically active phenethylamine, reduction of the imine with sodium borohydride, followed by hydrogenolysis to give the desired product. The instant invention claims fluorine and trifluoromethyl substitution on the substituted phenethylamine produced. A method of purification of the 2° amine intermediate is also claimed.

Bringman teaches (Page 2, line 65- page 3, line 46) the synthesis of an optically active phenyl-substituted phenethylamine via the formation of the imine (Schiff's base) by reaction of a ketone and optically active phenethylamine, reduction of the imine with hydrogen and a catalyst, followed by hydrogenolysis to give the desired product. Bringman further teaches (Page 3, lines 19-20) the hydrogenolysis of the 2° amine (reduced Schiff's base) at temperatures of 0-50 °C and pressures of 0-300 bar. Bringman exemplifies (Page 4, line 46 - Page 5, line 25; see Table experiment 10) the synthesis of the 2-fluorophenyl compound by hydrogenolysis of its acetate salt in methanol. The examiner notes that the corresponding processes that produce positional isomers about the phenyl ring are *prima facie* obvious over that taught by Bringman.

Bringman is silent with regard to the use of borohydride reducing agents to reduce the Schiff's base and with regard to trifluoromethyl substitution in the product.

Van Wagenen, however, teaches (Column 14, line 50 – column 15, line 12) a genus of compounds that have the structure of instant general formula [4]. Van Wagenen, teaches (Column 13, lines 11-25) a preferred embodiment of the following structure:



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where n= 1-5; X may be F or CF₃; and R= H or CH₃. Where R = CH₃ this structure then corresponds to the reduced Schiff's base intermediates of the instant claimed process. Van Wagenen further teaches (Column 30, lines 43-48) a general method of synthesis of these and related compound which proceeds through formation of a Schiff's base between a ketone and an amine and reduction to the 2^o amine with sodium borohydride. Van Wagenen further teaches (Column 32, lines 20-38) that compounds of the general structure taught can be converted to the hydrochloride salt and recrystallized as a method of purification.

Thus the instantly claimed invention would have been obvious to one of ordinary skill in the art. The motivation would have been to extend the utility of the process taught by Bringman to the synthesis of compounds for which the intermediates are taught by Van Wagenen. The process of Bringman is further improved by use of the borohydride reduction as taught by Van Wagenen. The expectation for success would have been near certitude since Van Wagenen teaches the intermediates required for the process of Bringman.

Examiner's Response to Applicants' Arguments with Regard to This Rejection

8. Applicants have put forth several arguments with regard to this rejection. The examiner responds to these below:
 - a. Applicants argue that the instant process is a position selective hydrogenolysis (Applicants' emphasis). The Examiner agrees that the hydrogenolysis is position selective with regard to which stereogenic carbon atom in the starting material undergoes N-C bond scission. There is,

however, no evidence on record that there is any positional selectivity for substituents about the aromatic rings.

- b. Applicants' arguments with regard to electronic and steric effects of substituents on the aromatic ring appear to be invented based on the list of substituents and their corresponding yields found in the table on page 5 of Bringman. As far as the Examiner is able to determine there is no basis in this simple list for Applicants' conclusions. The Examiner requests that Applicants point to where their position with regard to this issue finds support in Bringman. In fact, Beispeil Nr 6 (96% yield) demonstrates that an ortho positioned substituent is not required.
- c. Applicants further argue that strong electron attracting groups such as trifluoromethyl are not suggested. Bringman teaches (page 4, line 29) electron withdrawing alkoxy carbonyl substitution. Aside from the uncertain probative value of the electronic nature of the trifluoromethyl group, the Examiner agrees with Applicants that Bringman does not suggest the trifluoromethyl group. Bringman, however, clearly teaches fluorine substitution at arbitrary positions about the aromatic ring (although, as pointed out by Applicants, only ortho substitution is specifically disclosed).
- d. Applicants' arguments with regard to the structures of Van Wegenen do not appear to be particularly relevant to the issues under consideration since Van Wegenen was relied upon only for his teaching of the use of hydride reducing

agents in the reduction of the Schiff's bases to form the starting materials for the hydrogenolysis reaction.

- e. Applicant argues that Van Wegenen shows a compound which contains a 1-naphthyl group therefore claim 26 should be allowable. As discussed above Van Wegenen is relied upon only for the process of producing the hydrogenolysis substrate and appears to have little relevance in this context.
- f. Applicants' argue that Applicants' discovery that conducting the reaction at a modestly higher temperature allows one to conduct the reaction at a greatly reduced catalyst/substrate ratios and pressures renders claims 4 and 25 patentable. The Examiner agrees and has indicated such below.
- g. Applicants argue with regard to claim 2 that Van Wegenen teaches the use of sodium triacetoxyborohydride for reducing imines and not sodium borohydride. The Examiner disagrees and directs Applicants' attention to Van Wegenen who teaches (Column 30, lines 43-51, lines 47-48 specifically) the use of sodium borohydride. The structural variety disclosed by Van Wegenen underscores the generic nature of the imine reduction taught.
- h. Applicants argue that only the free base was crystallized not the hydrochloride salt. The Examiner disagrees. The hydrochloride salt was precipitated, and isolated, from ethereal solution. This constitutes a crystallization.

i. Applicants further argue that the specific acids of claim 9 are not taught by Van Wegenen. The Examiner disagrees. Hydrochloric acid, as discussed above, is specifically listed in claim 9.

Applicant's arguments filed 4 November 2002 have been fully considered but they are not persuasive for the reasons indicated above.

9. Claims 10, 11 and 13 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Hagitani et al (JP 09-278718 10-1997).

The instantly claimed invention is a method for the purification of optically active fluoro- and trifluoromethyl- substituted phenethylamines by formation of the corresponding mandelic or tartaric acid salt followed by recrystallization.

Hagitani teaches (Machine translation, page 5, lines 1-10) a method of purification of disubstituted phenethylamines which proceeds through formation and recrystallization of the mandelic acid salt. Hagitani further teaches (Machine translation, page 3, lines 30-33) disubstituted phenethylamines in which the substituents can be halo (fluoro) and fluoroalkyl (trifluoromethyl). Hagitani specifically teaches (Machine translation, page 3, line 42) 3-fluorophenyl substitution.

Thus the instantly claimed process would have obvious to one of ordinary skill in the art. The motivation would have been to apply the method for purification of

disubstituted phenethylamines taught by Hagitani to the purification commercially important compounds. The expectation for success would be near certitude since Hagitani teaches that the instant compounds are within the scope of his invention.

Examiner's Response to Applicants' Arguments with Regard to This Rejection

10. Applicants argue that Hagatani teaches only the purification of racemic material and that therefore claim 10 and its dependents 11 and 13 should be allowed. In fact Hagatani teaches (Machine translation, page 4, lines 1-2) the use of non-racemic (and therefore optically active) mixtures of 1-phenyl ethylamines. Notwithstanding this teaching, however, the purification of an optically active 1-phenylethylamine from an enantiomeric impurity remains obvious over Hagatani's purification of 1-phenylethylamines from their racemic mixtures.

Applicant's arguments filed 4 November 2002 have been fully considered but they are not persuasive for the reasons indicated above.

Claim Objections

11. Claims 4, 25 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter

12. Claims 4, 25 and 27 are drawn to allowable subject matter. The following is a statement of reasons for the indication of allowable subject matter: The processes for production of an optically active 1-(fluoro or trifluoromethyl substituted phenyl)

ethylamine) incorporating the limitations of instant claims 4, 25 and 27 are neither disclosed nor fairly suggested by the closest prior art of record: Bringman et al (DE 3819438-A1 01-1989), Van Wagenen et al (US 6,211,244-B1 04-2001) and Hagitani et al (JP 09-278718 10-1997). Claims 4 and 25 limit the process to temperatures higher than that taught by Bringman. Use of the higher temperatures results in the unexpected advantage that the reaction can be carried out at much lower pressures and catalyst loadings than would be expected based on the teaching of Bringman. Claim 27 requires the presence of a trifluoromethyl group in the hydrogenolysis substrate. The trifluoromethyl group was not suggested by Bringman. The success of the hydrogenolysis reaction of the substrate containing it could not have been predicted on the basis of Bringman.

Conclusion

13. Claims 1-13 and 25-28 remain pending. Claims 1-3, 5-13, 26 and 28 are rejected.

Claims 4, 25 and 27 are objected to.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and

any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
Patent Examiner
Technology Center 1600
January 9, 2003



ACTING FOR
Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
Technology Center 1600